The target organ damage in hypertension - the link to worse prognosis of COVID19 patients

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Abstract

From the report of the first case of COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) in December 2019 from Wuhan China, by June 1st 2020, 8.596.037 confirmed cases worldwide have been reported. Hypertension (HT) appears to increase the severity of COVID-19 and mortality risk both directly and indirectly. The immune system plays an important role in hypertension and hypertension-mediated organ damage. The invasion of SARS-CoV2 into the organism of a hypertensive patient, which already has a deleterious inflammatory immune response, can therefore more easily drive a quicker and exacerbated inflammatory response, leading more often, through cytokine storm, to severe ARDS forms, with worse prognosis for COVID-19 hypertensive patients.

Keywords: Hypertension, COVID-19, SARS-CoV2, Inflammation, Prognosis.

Introduction

From the report of the first case of COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) in December 2019 from Wuhan China, by June 1st 2020, 8.596.037 confirmed cases worldwide have been reported [1].

SARS-CoV2 cellular receptor that mediate entry into host cells is the angiotensin-converting enzyme 2 (ACE2) receptor, which is enriched in alveolar epithelial type II lung cells as well as in extra-pulmonary tissues such as heart, endothelium, kidneys and intestines, having an important role in the multi-organ effects of SARS-CoV2 infection[2,3]. What was initially thought to cause only a respiratory disease, varying in severity from paucisymptomatic patients to severe ADRS patients, current evidence indicates that SARS-CoV2 can also have adverse effects on cardiovascular, cerebral, renal and gastrointestinal system, as there is evidence of reports of cardiogenic involvement in patients without CVD as well as cases with solely cardiac presentations[2-7].

A large mata-analysis of over 46.000 COVID-19 confirmed cases reported by Zhou et al found that the most common co-morbidities were hypertension (HT) – 17%, diabetes 8% and cardiovascular diseases – 5%. What is of outmost importance is

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the reporting of more prevalent HT among severe cases (OR of 2.36) and in non-survivors – 48% [8]. Hypertension (HT) appears to increase the severity of COVID-19 and mortality risk both directly and indirectly.

Indirectly, the infection-containment measures imposed by all the Governments across all European Countries have substantial short and long-term consequences on hypertensive disease progression. The imposed quarantine, especially in older adults (above 65 years, an age segment in which HT's prevalence is high) favours sedentary and other unhealthy lifestyles, with negative impact both on HT's control in hypertensive patients and in HT's incidence. The cancelling of non-urgent outpatients visits required in order to ease the burden on health-care providers confronted with the increase in COVID-19 patients during the pandemic, have negatively impacted routine management of HT patients, the screening and early diagnosis of new-onset HT, medication adherence and therefore favouring, through uncontrolled HT, hypertensive-mediated organ damage (HMOD) onset and progression.

So, there are currently multiple ways in which SARS-CoV2 infection hit the hypertensive patients, leading indirectly to the increase in their morbi-mortality. In this way, the COVID-19 Pandemic also has substantial long-term impact on hypertensive patients across the World.

While controlling the SARS-CoV2 infection rates and minimize the number of infected individuals is an important target, long-term effect on HT is also of utmost importance, the pandemic could thus potentially affect QALY (Quality Adjusted Life Years) of hypertensive patients, making the socio-economic impact of HT on the healthcare system even worse. There are almost 94M individuals aged over 65 years (almost 19% of the entire world population) with an estimated HT's prevalence of over 40% [9,10].

The recent evidence of the role of immune dysregulation in hypertension may provide a possible explanation why a more severe course of COVID-19 is frequently encountered in hypertensive patients.

Both hypertension and hypertension-mediated organ damage onset and progression, are driven by inflammatory immune disbalance[11,12].

The over-activation of sympathetic nervous system (SNS) that pays a core-stone role in hypertension, has pro-inflammatory effects, since innervates the bone marrow, spleen, and peripheral lymphatic system [11-14]. The result in cytokine release will further enhance the SNS activity through their central nervous system action, that in turn will increase the mobilization, migration and infiltration of immune cells into the organs, where will trigger end-organ lesions [11-14].

While the worse prognosis in COVID 19 patients is associated with the increase in interleukin (IL) – 2, IL6, IL7, GCSF, CXCL10, CCL2 and TNFα, in what is so called cytokine storm, the same cytokines are known to be associated with the development of HT in both experimental and interventional studies [15-19].

Of those cytokines, IL6, which appears to be strongly linked to the clinical outcomes of SARS-CoV2 infected patients, is one of the key cytokines regulation immune-inflammatory responses in HT[11, 15,20-22].

HT is also causally associated with lymphocyte abnormalities [11,15], while lymphopenia is a known key feature of COVID-19 [2,20]. Also CD4+ and CD8+ are dysregulated in hypertension demonstrating greater production of pro-inflammatory cytokines, including those COVID-19-related ones (IL6, IL7, IL17, IFNγ and TNFα). More, HT is associated with a immunosenescent profile of CD8+ cells which are prone to overproduction of cytokines and are less efficient in antiviral defence [11, 15, 21-24].

Angiotensin II (Ang II) is a major mediator of hypertension and HMOD, not only by its vasoactive effects but also by increasing the expression of proinflammatory cytokines by its action on Ang II type 1 receptors (AT1R) on immune cells, especially IL-6 [11, 25-28].

Hypertensive vascular remodelling is driven by immunity, as the adventitia and perivascular adipose tissue are infiltrated macrophages and other inflammatory immune cells. These cells together with resident cells of the vessel wall produces cytokines and reactive oxygen species leading to vascular remodelling, as a result of an inflammatory state [11,29].

Complement factors are major pro-inflammatory component of the immune system, and their activity correlates with levels of Ang II and systolic blood pressure. Complement factor C3 induces proliferation of vascular smooth muscle cells, also contributing to the hypertensive vascular remodelling [11,30-32].

Hypertrophic cardiac remodelling in hypertensive patients is the results of not only the pressure overload, but also an inflammatory response of in situ or migratory immune cells such as CD4+ and CD8+ cells [11,33-35].

That is why altered immune-inflammatory response in HT may be the possible explanation for a more severe course of COVID-19 in hypertensive patients, especially in those who experience HMOD.

Nevertheless, there may be also the potential of a direct damaging effect of SARS-CoV2 on the organs.

One possible mechanism of cardiac damage in COVID-19 is represented by the opportunity for ACE2-dependent direct myocardial infection, since

ACE2 receptors are highly expressed in the heart. A second mechanism is related to the cytokine storm and the hypoxic state that characterises the severe ARDS form of COVID-19, that through excessive extracellular calcium levels may trigger myocyte apoptosis. Third, increased myocardial demand during the setting of an acute illness like COVID-19, together with the surge in cytokine levels, lead to atherosclerotic plaque instability and myocardial injury, increasing the risk of acute myocardial infarction [3, 36-39].

Acute kidney injury (AKI) was also reported in COVID-19 patients accompanying sepsis, MSOF and shock, suggesting acute tubular necrosis to be its cause, without excluding the plausibility of direct cellular damage from SARS-CoV2 through ACE2 receptor which was proved to be expressed in kidney cells. Where or not kidneys of hypertensive patients that exhibits different stages of hypertensive nephropathy are more prone to AKI during SARS-CoV2 infection remains to be confirmed [3, 40-42].

Viral invasion of the central nervous system (CNS) by SARS-CoV2 may be possible by synapse-connected route, observed in other coronaviruses such as SARS-CoV, leading to severe neurological complications including ataxia, seizures, neuralgia, unconsciousness, acute cerebrovascular disease and encephalopathy. Also potential CNS viral invasion might play a partial role in the pathophysiology of acute respiratory failure in COVID 19 patients [3, 43,44].

SARS-CoV2 infection also affects the progression of HMOD through the inflammatory response triggered by the virus itself. That is why also a long term negative effect on individuals with HT, linked to HMOD progression, is expected to be significant, since there is no clear evidence that once cured of COVID-19, the viral expression will be 100% cleared from the organism or it continues to persist thus self-sustaining an inflammatory response [45].

Conclusions

The immune system plays an important role in hypertension and hypertension-mediated organ damage. Also, the increased sympathetic activity driven by the stimulation of CNS resulting from a dysregulated inflammatory immune response, leads to the mobilization of inflammatory cells from the bone marrow and spleen into the heart, kidneys, arterial wall and CNS where they trigger and support the end-organ damage seen in hypertension.

The invasion of SARS-CoV2 into the organism of a hypertensive patient, which already has a deleterious inflammatory immune response, can therefore more easily drive a quicker and exacerbated inflammatory response, leading more often, through cytokine storm, to severe ARDS forms, with worse prognosis for COVID-19 hypertensive patients.

Keeping in mind that both HT and COVID-19 are diseases in which severity is driven by the inflammatory immune response, RAAS blockers such as ACEIs and ARB, throughout their benefits of: counteracting AngII proinflammatory effects, positive modulation of RAAS between ATII – AT1R axis, that is associated with injury of several organs including the lungs, and ACE2/AT 1-7/Mas R axis that counterbalance the AngII – AT1R axis protecting against tissue injury in the lungs, cardiovascular and renal systems, may offer protection from severe forms of COVID-19 rather than increase the risk of SARS-CoV2 infection or worsen the prognosis. That is why they should be continued in hypertensive patients in whom their used is recommended, expecially in those that associate hypertensive-madiated organ damage

Conflict of Interest

The author confirms that there are no conflicts of interest.

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